

The University of Chicago

A STUDY OF INTERACTION OF
CYANOGEN BROMIDE AND UNSATU-
RATED COMPOUNDS ESPECIALLY
OF ENOLIC TYPE

A DISSERTATION SUBMITTED TO THE FACULTY
OF THE DIVISION OF THE PHYSICAL SCIENCES
IN CANDIDACY FOR THE DEGREE OF DOCTOR
OF PHILOSOPHY

1932

By
BENJAMIN LEO MAIZEL

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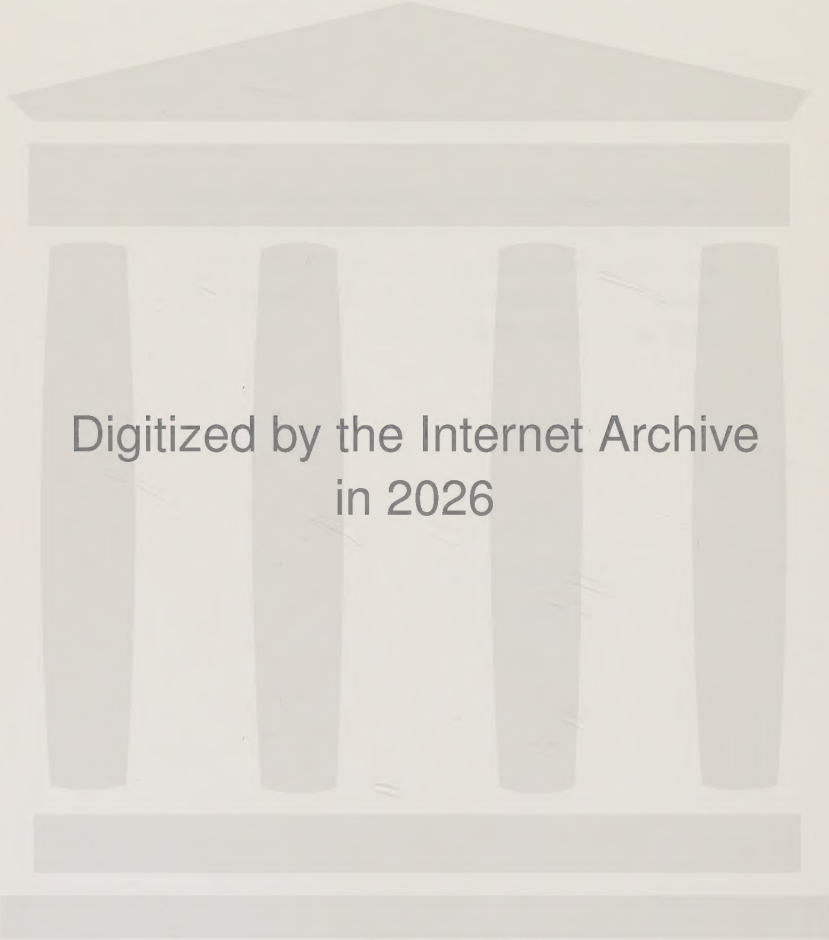
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ACKNOWLEDGMENT

I wish to express my sincere appreciation for the inspiration and guidance of Professor Stieglitz during the course of this work. I am indebted to R. W. Johnson for many a helpful suggestion.



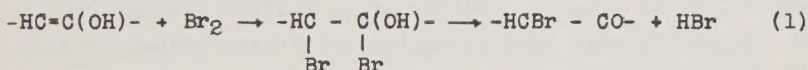
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INTRODUCTION

Many investigators have established that the enol form takes the active part in the bromination reactions involving keto-enol tautomers.¹ It is generally assumed that the first step in these reactions is the addition of a bromine molecule to the enolic double bond.² Stieglitz³ pointed out that simultaneous addition of both components of the absorbed molecule to the unsaturated carbon valences is quite doubtful and in fact unlikely.

K. Meyer⁴ and his students proved that only the enol form of acetoacetic ester reacts with bromine to give brominated acetoacetic ester. He assumes that the mechanism of substitution of bromine in acetoacetic ester, and in all compounds which can form keto and enol tautomers, is as follows:



To support this assumption Meyer cites the work of Lippmann⁵ who reported no evolution of hydrogen bromide when acetoacetic ester dissolved in ether was treated with bromine. Since ether forms

¹Reactions of acetone: Lapworth, J. Chem. Soc., 85, 30 (1904); Dawson and others, 95, 1940 (1909); 97, 2048 (1910); 105, 1275 (1914).

Reactions of α - and γ -ketonic acids: Hughes and Watson, ibid., (1929), 1945.

Reactions of aliphatic acids: Hill and Muhlhauser, Ber., 12, 727 (1879).

Reactions of phenols: K. Meyer, Ann., 398, 51 (1913).

²Nef, Ann., 266, 59 (1891); 276, 209, 235 (1893).

Willstätter and others, ibid., 378, 122 (1910); Ber., 41, 2202 (1909).

Lippmann, Zeit. für Chem., 5, 29 (1869).

³J. Amer. Chem. Soc., 44, 1304 (1922).

⁴Ann., 380, 220 (1911); 398, 46 (1913); Ber., 44, 2718 (1911); 45, 2843 (1912).

⁵Loc. cit.

stable oxonium salts with hydrobromic acid, no postulation of an intermediate addition compound is necessary to explain this observation. On the other hand, Nef states that there is immediate and vigorous liberation of hydrogen bromide even when acetoacetic ester is brominated at -15° . Similarly, Duisberg¹ was unable to obtain evidence for the presence of an addition compound of bromine and acetoacetic ester.

In 1893 Nef² claimed that he had obtained an addition compound when O-acetyl acetoacetic ester was treated with bromine at -15° . However, he based his conclusions on the study of the breakdown products rather than on determination of the properties of the substance itself.

Linneman³ stated that acetone forms an addition compound with bromine, but the later workers were unable to duplicate his results. The intermediate addition compound should be more unstable than the parent enol, and no one as yet has been able to isolate the enol form of a simple ketone.

Willstätter⁴ assumed that a ketone of a formula $C_{15}H_{30}O$ and cholestanone form addition products when treated with small quantities of bromine. But since he did not determine the solubility of hydrogen bromide in the solutions studied, the evidence is not conclusive.

Various theories have been formulated which explain the mechanism of formation of brominated enol compounds without assuming the preliminary addition of bromine to the enol double bond.

Thus, Steinkopf⁵ interprets the bromination reactions of cyanogen bromide on the basis of Pfeifer's⁶ "halochrom" theory. He assumes that the keto form reacts to give a molecular compound which splits off hydrogen cyanide. However, K. Meyer has shown that the keto form of acetoacetic ester does not react with bromine, and his results are probably also applicable to the reactions of acetoacetic ester with cyanogen bromide.

The study of brominations of fumaric acid in the presence

¹Ann., 213, 137 (1882).

²Ibid., 276, 206 (1893).

³Ibid., 125, 307 (1863).

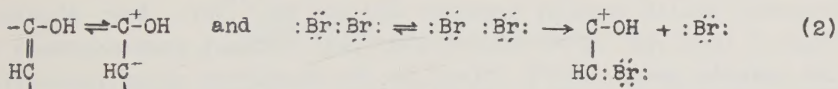
⁴Ibid., 378, 128 (1910); Ber., 41, 2202 (1908).

⁵Ann., 430, 75 (1923).

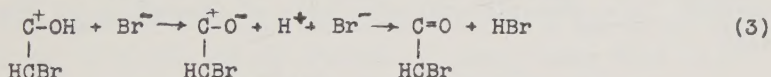
⁶Ibid., 376, 285 (1910); 383, 92 (1911).

of excess of chloride ion by Terry and Eichelberger,¹ and of ethylene by Francis,² led to the conclusion that these brominations occur in several steps. The entire bromine molecule, or the positive bromine atom, adds to the negative end of the double bond, leaving the free positive valence on the other carbon atom open for a competitive reaction with all negative ions present in the solution.

The bromination of the acetoacetic ester may be explained in a similar manner. The first step of the reaction should be the formation of an addition compound of bromine with one end of the double bond:³



This leaves the adjacent carbon with a free positive valence. As is well known, the enolic compound is slightly ionized, so that the intermediate steps may be written as follows:



There seems to be no fact which disagrees with the hypothesis that the intermediate positive valence is not satisfied in the manner indicated.

The present investigation was carried out at the suggestion and under the direction of Dr. Stieglitz, in order to ascertain, if possible, whether or not intermediate addition compounds are formed during the bromination of the enolic compounds.

Since no addition compounds of a halogen and of a substance having an enolic double bond have ever been isolated, a pseudo halogen, cyanogen bromide was chosen for this investigation. Benzene, naphthalene,⁴ phenol,⁵ thiophene, acetoacetic

¹J. Am. Chem. Soc., 47, 1067 (1925).

²Ibid., 47, 2347 (1925).

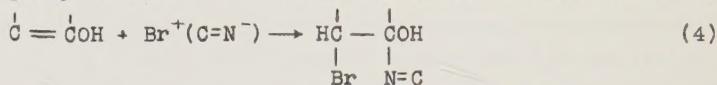
³Charges written in heavy type represent the ionic charges as in Na⁺Cl⁻. Those written in thin type (+ and -) represent the polarity of doublet electron valences as in A⁺B⁻, representing A :B. See Stieglitz, ibid., 44, 1296 (1922).

⁴Merz and Weith, Ber., 10, 746 (1877).

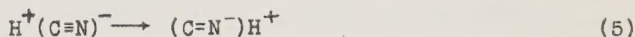
⁵Scholl and Nörr, ibid., 33, 1555 (1900).

ester and malonic ester,¹ have all been brominated with the aid of cyanogen bromide. No addition compound of cyanogen bromide with ethylene has ever been isolated; but even iodine, which is a true halogen, adds to ethylenic double bonds with a comparative difficulty. The fact that cyanogen bromide has an energy of activation twice as high as that of iodine may be the explanation of its lack of reactivity.

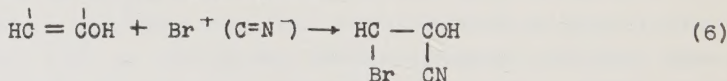
If we assume that cyanogen bromide under suitable conditions might form addition products with double bonds, especially of enolic type, then the following considerations must be kept in mind. The form active in brominations must be $(C=N^-)Br^+$ (more properly called bromine cyanide) and not $Br^-(^+CN)$. Now, absorption of $(C=N^-)Br^+$ by an enol would lead, without rearrangement of the cyanide group $(C=N^-)$, first to the formation of an isonitril:



However, in a strictly analogous case of absorption of hydrocyanic acid



by aldehydes and ketones, the active acid form is undoubtedly $(C=N^-)H^+$ but the structures of the products of absorption represent true nitrils $\begin{array}{c} \text{C} \\ | \\ \text{C}-\text{CN} \\ | \\ \text{OH} \end{array}$. These relations are already well established for hydrocyanic acid and may be applied without qualifications to its derivative cyanogen bromide. Therefore, if addition occurs, the tangible product of the action of cyanogen bromide on an enol would be a true cyanohydrin

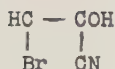


Compounds of this type should be relatively stable and in suitable instances it should be possible to prepare them also from bromoketones and hydrogen cyanide and thus prove their structure.

Summarizing, the purpose of this investigation has been:

1. To discover, if possible, whether cyanogen bromide adds to double bonds.
2. To prepare cyanohydrins of the type

¹Steinkopf, Ann., 430, 48 (1923).



from suitable ketones and hydrocyanic acid.

3. To see whether the same compounds could be isolated from a reaction mixture in which the unbrominated ketones were allowed to react with cyanogen bromide.

4. To show that the cyanohydrins of this type are stable under the conditions of the experiment, and, that if they were formed, it would be possible to demonstrate their presence.

DISCUSSION OF THE RESULTS

Inasmuch as the keto-enol tautomerism of acetoacetic ester had been studied in great detail by various workers, this substance was chosen as the first compound for the investigation.

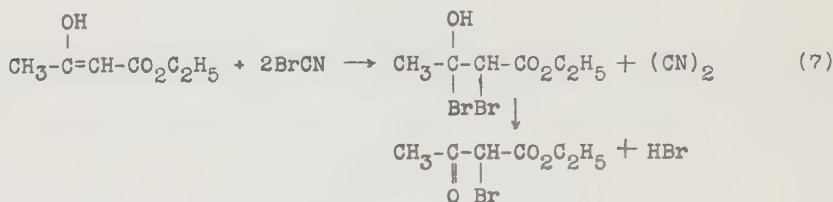
The cyanohydrin of α -bromoacetoacetic ester was prepared by the treatment of α -bromoacetoacetic ester with anhydrous hydrogen cyanide, a little sodium acetoacetic ester being used as a catalyst. In earlier experiments potassium cyanide was used as a catalyst, but the resulting product was a dark brown oil which decomposed easily on being heated. The cyanohydrin obtained with the aid of sodium acetoacetic ester was much easier to purify.

Acetoacetic ester was next brominated with cyanogen bromide in the presence of phosphorus pentoxide. Ultee¹ pointed out that he was able to distil certain cyanohydrins only after they were stabilized by addition of a little concentrated sulphuric acid. Phosphorus pentoxide has a similar inhibitory effect on the decomposition of the cyanohydrins. Furthermore, the experiments have shown that the reaction between cyanogen bromide and ketones was accelerated by the presence of phosphorus pentoxide.

Whenever the reaction between acetoacetic ester and cyanogen bromide was carried out in an acid or a neutral solution, the only products isolated were α - and γ -bromoacetoacetic esters. Not even a trace of nitrogen containing compounds was found in either residue or distillate after the reaction mixture had been distilled in vacuo. In the control experiments in which 0.01 gm.

¹Rec. Trav. Chim., 28, 1 (1909).

of the cyanohydrin of α -bromoacetoacetic ester had been added to the reaction mixture, a very strong test for the cyanide group was obtained in the residue after distillation. This proved quite conclusively that no cyanohydrin was formed during the reaction. A possible, although rather unlikely, mechanism for the reaction of cyanogen bromide with acetoacetic ester is as follows:



To test this possibility, the gases liberated during the reaction were tested for cyanogen, hydrocyanic acid and hydrobromic acid. No evidence of the presence of cyanogen was found in any of the experiments, but the amount of hydrocyanic acid evolved was nearly 90 per cent of the theoretical. Hence the reaction does not proceed according to the mechanism indicated above.

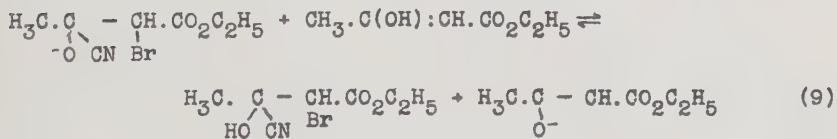
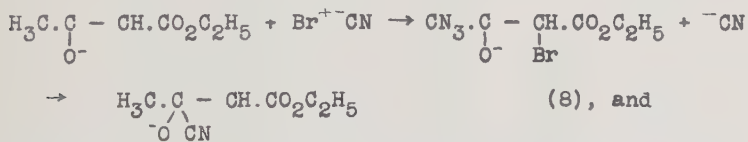
In order to make certain that the non-formation of the cyanohydrin of bromoacetoacetic ester was not due to an insufficient amount of the reactive enol form, acetoacetic ester was mixed with three times its weight of hexane and then treated with cyanogen bromide. According to the work of Knorr, Rothe, and Averbeck,¹ a saturated solution of acetoacetic ester in hexane is enolized to the extent of 30 per cent, and the equilibrium is attained in about sixty minutes. Since forty-eight hours proved necessary to obtain about 50 per cent of the theoretical yield of α -bromoacetoacetic ester, there was ample time for the formation of more enol as it was consumed in the reaction. In spite of these favorable factors, not a trace of the cyanohydrin was found.

When a suspension of copper acetoacetic ester in chloroform was treated with cyanogen bromide, an almost instantaneous reaction took place, with a considerable evolution of heat. The product formed was again α -bromoacetoacetic ester. The difference in the reaction rates of the salt and the ester is so great that it seems altogether probable that the active form is not the enol form as such, but rather its ion. No cyanohydrin was found in

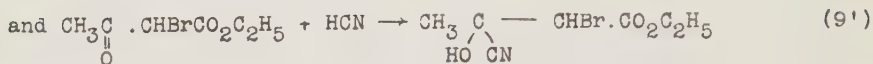
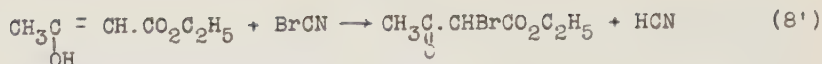
¹Ber., 44, 1138 (1911).

the product of this reaction. Control experiments showed that the cyanohydrin of α -bromoacetoacetic ester may be recovered under the experimental conditions used if a small quantity of it is added to the reacting mixture. It is evident that no cyanohydrin was formed and bromination was the only action completed. In considering this result it should be borne in mind that cuprous cyanide, $\text{Cu}_2(\text{CN})_2$, and its complex ion, $\text{Cu}(\text{CN})_2^-$, are extraordinarily stable. As a result, the cyanide ions liberated from cyanogen bromide by the bromination of the ion of cupric acetoacetic ester would be suppressed by the cupric ions before they could attach themselves to the α -carbonyl group of acetoacetic ester. Thus, the formation of a cyanohydrin would be prevented.

The validity of this argument is borne out by the results of the treatment of acetoacetic ester with cyanogen bromide in the presence of a small amount of sodium acetoacetic ester. Both α -bromoacetoacetic ester and its cyanohydrin are obtained in good yields. The formation of cyanohydrin in quantity under these conditions indicates that it is the product of the unimpeded absorption, in sequence, of Br and CN by the ion of acetoacetic ester, expressed as follows:



It is also true that α -bromoacetoacetic ester reacts very speedily with hydrocyanic acid under the conditions of the experiment. It is necessary, therefore, to consider the possibility that the formation of the cyanohydrin is not the result of an addition of cyanogen bromide to the double bond of the enolate ion but starts with the formation of bromoacetoacetic ester and the liberation of hydrogen cyanide, which then combine to form the cyanohydrin:



Since the reaction is catalyzed by the presence of sodium acetoacetic ester, there is no doubt that it is its ion and not the enol itself, that reacts with cyanogen bromide. Hence, there would be no hydrogen ion immediately available for the production of hydrocyanic acid, as required by equation (8'). Furthermore, if the latter were formed, it would have to ionize again into H and CN to be absorbed by the carbonyl group. Consequently the picture in equations (8) and (9) of the formation of the cyanohydrin of α -bromoacetoacetic ester from the acetoacetic ester ion by the direct absorption, in sequence, of the components of cyanogen bromide, seems to us the correct interpretation of the reaction. These equations also show that the reacting enolate ion of acetoacetic ester is regenerated (equation 9) and hence the catalytic effect of the presence of a small amount of sodium acetoacetic ester is to some extent a chain reaction.

Critical analysis of this reaction leads, therefore, to the conclusion that in the formation of the cyanohydrin of α -bromoacetoacetic ester we have a true instance of the type of reaction we have sought to find, namely, a consummated addition reaction of cyanogen bromide to an enolate double bond. Taken in conjunction with the contrasting behavior of cupric acetoacetic ester toward cyanogen bromide, it is equally evident that the addition to the enolate double bond takes place in two steps, the primary addition of Br^+ to the negative end of the double bond, and the secondary addition of CN to its positive end. This composite character of the addition reaction accounts also for the formation of α -bromoacetoacetic ester, in good yield, side by side with its cyanohydrin, in good yield, in the action of cyanogen bromide on acetoacetic ester in the presence of a little sodium salt of the ester: when the action stops with the primary addition of Br^+ to the enolate ion (equation [8]), as it well might, bromoacetoacetic ester would be the product of the action.

The evidence that the addition reaction does take place in two steps is in complete agreement with the views of the one of us (see p. 1) and with the later experimental confirmation of

this principle by Terry and Eichelberger and by Francis (see p. 3).

Cyanogen bromide seems to react to form an addition product with O-acetyl acetoacetic ester; but the acetyl group in that compound does not ionize, and the competitive reactions described in the equations (2) and (3) cannot occur. Therefore, an addition rather than a substitution product should be formed.

A study of the reactions of dibenzoyl methane with cyanogen bromide was undertaken next. When an ether solution of dibenzoyl methane was refluxed with cyanogen bromide for two days, monobromodibenzoyl methane, but no cyanohydrin was obtained. In the presence of a small quantity of sodium dibenzoyl methane the reaction went much more rapidly. Since in ether solution dibenzoyl methane is enolized to the extent of about 98 per cent, the slowness of the reaction in the absence of the sodium enolate cannot be attributed to an insufficient amount of enol form. Hence the increase in the speed of the reaction after the addition of the sodium salt points also to the fact that the enol ion rather than the enol itself is the active form in the reaction with cyanogen bromide. Not a trace of any nitrogen containing compound other than cyanogen bromide and hydrocyanic acid, was found in any of the experiments with dibenzoyl methane. Hence, the formation of a cyanohydrin by absorption had not occurred.

In order to determine how stable the cyanohydrin of dibenzoyl methane and of monobromodibenzoyl methane would be under the conditions of the experiment with cyanogen bromide, efforts were made to obtain the cyanohydrins directly by usual methods used for the preparation of cyanohydrins. All of the experiments attempted were unsuccessful. Therefore, it could not be determined whether the cyanohydrin, if formed as a primary product of the reaction between dibenzoyl methane and cyanogen bromide, would be stable under the conditions used. Bromination of dibenzoyl methane to monobromodibenzoyl methane was the only reaction definitely established.

Various authors¹ have postulated that the reactions of acetone with the halogens can be interpreted by assuming that they react with the enol form of acetone. The cyanohydrin of

¹Lapworth, *J. Chem. Soc.*, 85, 30 (1904).
Dawson and Powis, *ibid.*, 101, 1503 (1912).

bromoacetone was prepared by the method which Ultee¹ used to prepare the cyanohydrin of chloroacetone. It was identified by being hydrolyzed to β -bromo α -hydroxyisobutyric acid. When the cyanohydrin of bromoacetone was added to the mixture of acetone and cyanogen bromide, and the solution heated on the water bath in the presence of a trace of phosphorus pentoxide, it was possible to obtain from the reaction mixture about 50 per cent of the theoretical yield of bromoacetone, and to recover the added cyanohydrin almost quantitatively. In other experiments in which no cyanohydrin was added to the reaction mixture, only bromoacetone, and not a trace of cyanohydrin, was found after the reaction was complete. It is evident that cyanogen bromide brominates acetone but does not form addition products.

Except for the reaction of cyanogen bromide with acetoacetic ester in the presence of its sodium salt, all the experiments discussed show that substitution products only--and not even a trace of addition products--are formed as a result of treating the enol forming compounds with cyanogen bromide. The only exception, as stated, was the reaction of acetoacetic ester with cyanogen bromide in the presence of sodium acetoacetic ester, in which α -bromoacetoacetic ester, as well as its cyanohydrin, was formed. In view of the negative results obtained in regard to the formation of addition products in all the other reactions studied, the formation of the cyanohydrin in the case of acetoacetic ester may still be due to a secondary reaction between α -bromoacetoacetic ester and the hydrogen cyanide formed in the course of the reaction, as indicated above.

The next experiments were conducted in order to find out whether it is possible to add cyanogen bromide to ethylenic double bonds. The results obtained were uniformly negative. Ethylene, butadiene, amylene, allyl bromide, and allyl ether gave no evidence whatsoever of reacting with cyanogen bromide, even when attempts were made to activate the cyanogen bromide with the ultraviolet light from an iron arc. The reaction between allyl alcohol and cyanogen bromide yielded heavy viscous oils which on hydrolysis gave little or no acid of the type expected from nitrils.

In view of the failures to obtain the addition products with ethylenic double bonds, the problem of addition of cyanogen

¹Rec. Trav. Chim., 28, 17 (1909).

bromide to enol derivatives of the type $RO-C=CH-$ was next taken up. Cyanogen bromide was allowed to react with O-acetyl acetoacetic ester. The reaction mixture was distilled at the pressure of 1 mm. Since the boiling point of cyanogen bromide at 760 mm. is 62° , the distillate coming over at a temperature of 75° at 1 mm. could not possibly contain cyanogen bromide. Both the distillate coming over at that temperature and the residue from distillation gave definitely positive tests for bromine and for the cyanide group. The analytical figures for bromine and for the nitrogen were far too low for the pure nitril, but the presence of a removable cyanide group indicates a cyanohydrin, while liberation of iodine from a solution of potassium iodide is characteristic of α -bromoketones. Therefore, an addition compound of O-acetyl acetoacetic ester was probably formed.

The following conclusions may be drawn from the results obtained in this investigation:

1. Cyanogen bromide was found to react with all the compounds used, which were capable of enolization, to give brominated substitution products.

2. Except in a single instance (see #3 below), no addition products, brominated cyanohydrins, were obtained, although these brominated cyanohydrins, formed by the addition of hydrogen cyanide to some of the brominated carbonyl derivatives, were found to be stable under the conditions used and were easily detected when added to the products formed.

3. In only one instance, namely, in the action of cyanogen bromide on acetoacetic ester in the presence of a small amount of its sodium salt, was the addition product of the cyanogen bromide to the enolizable compound obtained in large yield, side by side with a considerable amount of the substitution product, -bromoacetoacetic ester.

4. It was shown that this addition product, the cyanohydrin of α -bromoacetoacetic ester, could have been formed under the conditions used as the result of a primary bromination to -bromoacetoacetic ester followed by the addition of liberated hydrocyanic acid to the brominated substitution product.

5. The evidence in favor of direct addition of cyanogen bromide to the double bond of the enol of acetoacetic ester is therefore not conclusive.

6. In any event bromination without addition of both

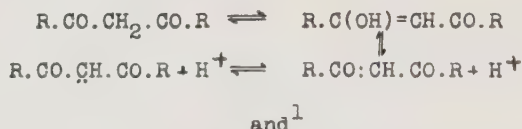
cyanogen and bromine groups to the double bond is the dominating characteristic of these reactions.

7. The evidence favors the conclusion that in these reactions the active form is the enolate ion rather than the enol or the keto molecules. It is altogether possible, and even likely, that the real reacting compound is the carbide ion formed by tautomerization of the enolate ion.

8. If the mechanism of the reaction of halogens and of cyanogen bromide with the enolic double bond are similar, then K. Meyer's assumption is incorrect that unstable intermediate saturated addition compounds are first formed when bromine reacts with enol to form brominated ketones.

9. Even if the assumption of similarity between cyanogen bromide and halogens is not granted, still it is no longer necessary or justifiable to postulate the formation of an intermediate addition product when an enolic compound reacts with a halogen. Cyanogen bromide is found to be capable of giving the same final products as those formed by bromine, without forming an intermediate addition compound.

10. On the basis of the evidence assembled and of the conclusions reached, the action of cyanogen bromide (and of bromine) on a typical enolizing compound $R.CO.CH_2.CO.R$ may be formulated as follows:



Similarly:²



¹The active molecules of cyanogen bromide are considered to have the structure $:\ddot{Br}: :C::N$ or $Br^+ \text{ } ^-CN$ (see p. 4 of the dissertation).

²The active molecules of bromine are considered to have the structure $:\ddot{Br}:\ddot{Br}:$ or $Br^+ Br^-$.

EXPERIMENTAL PART

I. REACTIONS OF ACETOACETIC ESTER

1. Cyanohydrin of α -bromoacetoacetic ester, $\text{CH}_3\text{C}(\text{OH})(\text{CN})\text{CHBrCO}_2\text{C}_2\text{H}_5$. The cyanohydrin of α -bromoacetoacetic ester was prepared by the method developed by Ultee¹ for the preparation of cyanohydrins. One gram of acetoacetic ester in which a trace of sodium was allowed to dissolve, was added to a mixture of α -bromoacetoacetic ester² (20 gm.) and anhydrous hydrocyanic acid (20 gm.) cooled to 0° . The mixture immediately darkened and became warm. After the reaction had subsided, 5 gm. of hydrocyanic acid was added to the solution, and the flask was placed in the ice box for four hours. The oil was then washed with dilute sulphuric acid, dried with sodium sulphate, and distilled. The fraction boiling on redistillation at 113° and 1 mm. was collected.

Upon being heated with alkali, the substance gave a positive test for the cyanide ion. When it was distilled at 3 mm. in the presence of alkali, a liquid boiling between 80° - 90° was obtained. It was identified as α -bromoacetoacetic ester by its thiourea derivative, amido-methyl thiazol carbonic ester, $\text{CH}_3\text{CNC}(\text{NH}_2)\text{SCCO}_2\text{C}_2\text{H}_5$ ³ m.p. 175° .

Analysis. Sbst.: 0.4651, 0.5214 gm.; 0.1N AgNO_3 , 19.19, 21.99 cc.
0.2125, 0.2892 gm.; 0.1N HCl , 12.86, 11.73 cc.
Calc. for $\text{C}_7\text{H}_{10}\text{O}_3\text{BrN}$: Br, 33.80%, N, 5.92%
Found: Br, 33.55, 33.80%; N, 5.75, 5.69%

2. Reaction of cyanogen bromide with acetoacetic ester. Acetoacetic ester (26 gm.) was mixed with cyanogen bromide⁴ (21.5 gm.). The solution was then divided into two equal parts, A and B. About 1 mg. of phosphorus pentoxide was added to each solution. About 0.05 gm. of the cyanohydrin of acetoacetic ester was

¹Rec. Trav. Chim., 28, 1 (1909).

²Conrad, Ber., 29, 1042 (1896). ³Ibid.

⁴Steinkopf, J. Pr. Chem., (2) 109, 347 (1925).

added to the solution B.

Each mixture was placed into a one piece refluxing apparatus. Calcium chloride tubes on the end of the condensers were connected with a train of two wash bottles; the first containing 50 cc. of acidified 0.5N silver nitrate and the second 50 cc. of 0.5N sodium hydroxide.¹ The reaction mixtures were heated on the water bath for five hours. Each silver nitrate bottle contained a copious white precipitate, which was composed of silver cyanide contaminated by a trace of silver bromide. It weighed, in each case, 12.8 gm., which accounts for 92 per cent of hydrocyanic acid that could be formed by the reaction



The presence of silver bromide was probably due to a small amount of cyanogen bromide which distilled over. The liquid in the sodium hydroxide bottles gave negative tests both for cyanide and cyanate ions; hence no cyanogen was evolved from the reaction mixture.

The products of the reaction were distilled at 3 mm. with the aid of an oil bath the temperature of which did not exceed 115°. Between 78° and 85°, 18 gm. of distillate was obtained from solution A and 16 gm. from solution B. The liquids were composed chiefly of α -bromoacetoacetic ester. The test for the cyanide group and for nitrogen by the sodium fusion test, was negative in each case. However, the residue from the distillation of the solution B gave a very strong test for the cyanide group, while the residue from solution A gave a negative test both for cyanide and for nitrogen.

3. Reaction of cyanogen bromide and acetoacetic ester in the presence of ligroin. Two 5 gm. portions of solutions similar to the ones used in the previous experiment were prepared, and 15 gm. of "Skellysolve B"² was added to each. They were heated on the water bath for two days. About 4 gm. of α -bromoaceto-

¹Cyanogen is not absorbed by silver nitrate, but is absorbed and decomposed by sodium hydroxide (Allen, "Commercial Organic Analysis," Blakiston's Sons & Co., Philadelphia, 1913, VII, 456, 539).

²"Skellysolve B," according to the Skelly Oil Company, consists chiefly of normal hexane.

acetic ester was obtained from each reaction mixture. Again, the residue only from solution B gave a positive test for cyanide or nitrogen.

4. Reaction of copper salt of acetoacetic ester with cyanogen bromide. The copper salt of acetoacetic ester¹ (48 gm.) was suspended in 200 cc. of carbon tetrachloride, and 25 gm. of cyanogen bromide was added to the mixture. The color of the suspension immediately was changed from green to brown and mixture became warm. The bottle was then placed in a shaking machine for twenty-four hours. The liquid phase was separated by centrifuging, and purified by distillation at 3 mm. Forty-one grams of distillate boiling between 75° and 85° was obtained. It was identified as α -bromoacetoacetic ester by its thiourea derivative. The test for the nitrogen was negative both on the distillate and the residue from distillation.

The sludge obtained from the centrifuging was identified as cuprous cyanide contaminated with cuprous bromide.

When the reaction was carried out in exactly the same manner, except that 2 gm. of the cyanohydrin of α -bromoacetoacetic ester was added to the original solution, the residue in the distilling flask gave a very strong test for the cyanide group.

5. Reaction of acetoacetic ester with cyanogen bromide in the presence of sodium acetoacetic ester. A small piece of sodium was dissolved in 26 gm. of acetoacetic ester and 21 gm. of cyanogen bromide was added to the solution. Immediately the solution became warm and the yellow color of sodium acetoacetic ester disappeared. The solution was allowed to stand in the ice box overnight. It was then washed with dilute sulphuric acid, and with water, dried with anhydrous sodium sulphate and distilled at 1 mm. The fraction boiling between 60° and 90°, which weighed about 10 gm., was composed chiefly of α -bromoacetoacetic ester. The fraction boiling between 90° and 115°, which weighed 28 gm., on redistillation gave 12 gm. of a product boiling at 113°. The substance gave a strong cyanide test, contained bromine, and liberated iodine from potassium iodide solution. It was therefore the cyanohydrin of α -bromoacetoacetic ester.

Analysis: Sbst.: 0.6848, 0.6351 gm.; 0.1N AgNO₃; 28.91, 26.93 cc.
0.4592, 0.3982 gm.; 0.1N HCl, 17.67, 15.44 cc.

¹Conrad and Guthzeit, Ber., 19, 21 (1886).

Calc. for $C_7H_{10}O_3NBr$; Br, 33.80%; N, 5.92%
Found: Br, 33.71, 33.85%; N, 5.39, 5.42%

II. REACTIONS OF ACETONE

1. Cyanohydrin of bromoacetone, $CH_3C(OH)(CN)CH_2Br$. The cyanohydrin of bromoacetone was prepared from bromoacetone and anhydrous hydrocyanic acid by the method developed by Ultee.¹ The substance is a colorless, pleasant smelling oil, boiling between 101° and 106° at 7 mm.

Analysis: Sbst.: 0.3946, 0.4618 gm.; 0.1N $AgNO_3$, 24.25, 28.40 cc.
0.3641, 0.3536 gm.; 0.1N HCl, 21.92, 21.15 cc.
Calc. for C_4H_8ONBr : Br, 49.04%, N, 8.56%
Found: Br, 49.1, 49.2%; N, 8.42, 8.38%

Ten grams of the compound was hydrolyzed at room temperature with 50 cc. of 1N sulphuric acid. The purified acid produced melted at 100° . The recorded melting point of isobromohydroxybutyric acid² is 100° - 101° .

Analysis: Sbst.: 0.2110, 0.1934 gm.; 0.1N $AgNO_3$, 11.42, 10.50 cc.
Calc. for $C_4H_7O_3Br$: Br, 43.68%
Found: Br, 43.80, 43.85%

2. Reaction of acetone with cyanogen bromide. Cyanogen bromide (20 gm.) was mixed with 30 gm. of acetone. The solution was divided into two equal parts A and B, and about 1 mg. of phosphorus pentoxide was added to each. One gram of cyanohydrin of bromoacetone was added to the solution B. Both solutions were heated on the water bath for two days under a reflux condenser.

Solution A was distilled at 12 mm. The distillation was completed below 50° , leaving the flask practically free from residue. The distillate consisted mainly of bromoacetone. Neither the distillate nor the residue in the flask gave a positive test for the cyanide group or for nitrogen.

Solution B was distilled at 7 mm. The major fraction came over at 28° - 35° , then the temperature rose rapidly, and 0.8 gm. of the substance distilled at 100° - 110° . This fraction gave a very strong test for bromine and for the cyanide group and evidently contained cyanohydrin of bromoacetone.

¹Loc. cit.

²Kay, J. Chem. Soc., 95, 561 (1909).

The entire reaction was repeated in an identical manner, except that no phosphorus pentoxide was used. The reaction was much slower, but otherwise the results were the same as before.

III. REACTIONS OF DIBENZOYLMETHANE

1. Attempts to prepare the cyanohydrins of dibenzoylmethane and of monobromodibenzoylmethane. All attempts to prepare the cyanohydrins of dibenzoylmethane and of monobromodibenzoylmethane were unsuccessful. The method of Ultee resulted in the formation of a dark brown gum. Heating the substances under pressure with anhydrous hydrocyanic acid produced no reaction. The original substances were also recovered unchanged, when Jacoby's method for the preparation of cyanohydrins was tried.¹

2. Reaction of dibenzoylmethane with cyanogen bromide. Dibenzoylmethane (10 gm.) was dissolved in 25 cc. of dry ether; cyanogen bromide (5 gm.) and 1 mg. of phosphorus pentoxide were added to the solution. The mixture was heated under a reflux condenser for ten days. By fractional recrystallization from ligroin crystals (7.5 gm.) melting at 92°-93° were obtained. This fraction was identified as monobromodibenzoylmethane by the melting point of a mixture of the product with a known sample of the derivative. Some gum unidentified and unchanged dibenzoylmethane were also isolated. The nonvolatile products of the reaction gave a negative test both for the cyanide group and for nitrogen.

3. Reaction of dibenzoylmethane with cyanogen bromide in the presence of sodium. Dibenzoylmethane (11 gm.) was dissolved in 59 cc. of ether and about 0.1 gm. of sodium was added to the solution. The metal dissolved with evolution of a gas, and a white solid precipitated out. When cyanogen bromide (6 gm.) was added to the mixture, it immediately became warm, and some of the solid went into the solution. The mixture was allowed to stand for two hours; then it was washed with water and dried with sodium sulphate. Monobromodibenzoylmethane and dibenzoylmethane were isolated from the reaction mixture by fractional crystallization. The wash water gave a strong test for free hydrocyanic acid. No evidence could be found for the presence of any other compound containing nitrogen.

¹Ber., 19, 1519 (1896).

Similar results were obtained when a sufficient amount of sodium was used to change all of the dibenzoylmethane into its sodium salt. A water soluble substance, m.p. 169° , which contained bromine, liberated iodine from potassium iodide solution, and gave a red coloration with ferric chloride, was also isolated in this reaction. Since it did not contain nitrogen, it was not studied any further.

IV. REACTIONS OF CYANOGEN BROMIDE WITH UNSATURATED ALIPHATIC COMPOUNDS

1. Butadiene and cyanogen halides. No reaction had occurred when butadiene was treated, respectively, with cyanogen chloride, bromide, and iodide at -5° . Illuminating the reaction mixture with a 500 W. Mazda lamp had no effect.

2. Ethylene and cyanogen bromide. No evidence of a reaction at room temperature between ethylene and cyanogen bromide was found, even when cyanogen bromide was illuminated with an iron arc through a crystal quartz window.

3. Amylene, allyl ether, allyl bromide, and cyanogen bromide. Cyanogen bromide was dissolved, respectively, in amylene, allyl bromide, and allyl ether. The solutions were heated under a reflux condenser for several days. In each case the original products could be recovered almost quantitatively. The addition of a trace of phosphorus pentoxide, and exposure of the reaction vessel to the rays of an iron arc produced no effect.

4. Allyl alcohol and cyanogen halides.¹ Heavy viscous oils were obtained when allyl alcohol, acidulated with gaseous hydrobromic acid, was heated under a reflux with cyanogen bromide or iodide. High boiling substances containing halogen and nitrogen were present in the reaction products. However, all attempts to isolate simple nitrils from these mixtures were unsuccessful.

5. Reaction of O-acetyl-acetoacetic ester with cyanogen bromide. O-acetyl acetoacetic ester was prepared by the method of Claisen.² The fraction boiling at 69° - 70° and 1 mm. was used.

Cyanogen bromide (10 gm.) and phosphorus pentoxide (1 mg.) were dissolved in 20 gm. of O-acetyl acetoacetic ester. The mix-

¹This work was done in co-operation with Miss R. Klaas.

²Claisen and Haase, Ber., 33, 1242 (1900).

ture was heated for two days under a reflux condenser on an oil bath at 125°. The solution was then distilled at 1 mm. The entire distillate came over between 77° and 81°. About 10 gm. distilled at 80°-81°. Both the distillate and the residue from the distillation gave definite tests for the cyanide group and for bromine, and liberated iodine from the solutions of potassium iodide. However, the analysis showed that the quantity of bromine and especially of nitrogen present in the liquid was very small.

Analysis: Sbst.: 0.4433, 0.4700 gm.; 0.1N AgNO₃, 5.41, 5.83 cc.
0.2174, 0.2575 gm.; 0.1N HCl, 0.36, 0.35 cc.

Calc. for C₉H₁₂O₄NBr: Br, 28.67%; N, 5.04%

Found: Br, 9.87, 10.01%; N, 0.23, 0.19%

SUMMARY

1. The cyanohydrin of α -bromoacetoacetic ester was prepared from α -bromoacetoacetic ester and hydrocyanic acid.

2. The cyanohydrin of bromoacetone was prepared from bromoacetone and hydrocyanic acid.

3. Reactions of cyanogen bromide with acetone, acetoacetic ester and dibenzoylmethane in the presence of a trace of phosphorus pentoxide, resulted in the formation of brominated products only. No evidence could be found for the formation of any nitrogen containing reaction products, although control experiments had shown that the presence in the reaction mixtures of 0.1 per cent of the cyanohydrin of acetone or of acetoacetic ester, respectively, could have been easily detected.

4. The reaction between the copper salt of acetoacetic ester and cyanogen bromide took place with very great speed and resulted in the formation of the bromine substitution product only. No cyanohydrin could have been formed since the control experiments had shown that, if formed, it would not have been decomposed under the conditions of the reaction.

5. The reaction between cyanogen bromide and acetoacetic ester in the presence of its sodium salt resulted in the formation of α -bromoacetoacetic ester and of cyanohydrin of α -bromoacetoacetic ester, both in large yields. The cyanohydrin may well have been formed by the direct addition of the cyanogen bromide to the double bond of the enolate ion of acetoacetic ester. It was shown, however, that the keto-form of α -bromoacetoacetic ester

and hydrocyanic acid might be the primary products of the action of cyanogen bromide on the enolate ion of the ester, and that these primary products would combine rapidly to form the cyano-hydrin.

6. No evidence of any action of cyanogen bromide on butadiene, ethylene, amylene, allyl bromide, or allyl ether was found. The components were recovered unchanged in the experiments tried.

7. Cyanogen bromide and allyl alcohol have been found to react with each other, but the exact nature of the reaction products has not been ascertained.

8. The reaction between O-acetyl acetoacetic ester and the cyanogen bromide leads to the formation of high boiling substances (80° - 81° at 1 mm.) containing a very small amount of nitrogen. This result is indicative of the formation of addition product of cyanogen bromide and O-acetyl acetoacetic ester, since other likely nitrogen derivatives, such as cyanogen bromide, hydrocyanic acid, acetyl bromide, etc., are much more volatile than the substances found.

9. The theoretical conclusions based on the above evidence were presented (pp. 11-12).

